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Ambrisentan Therapy for Pulmonary Arterial Hypertension

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OBJECTIVES The purpose of this study was to examine the efficacy and safety of four doses of ambrisentan, an oral endothelin type A receptor-selective antagonist, in patients with pulmonary arterial hypertension (PAH).

BACKGROUND Pulmonary arterial hypertension is a life-threatening and progressive disease with limited treatment options. Endothelin is a vasoconstrictor and smooth muscle cell mitogen that plays a critical role in the pathogenesis and progression of PAH.

METHODS In this double-blind, dose-ranging study, 64 patients with idiopathic PAH or PAH associated with collagen vascular disease, anorexigen use, or human immunodeficiency virus infection were randomized to receive 1, 2.5, 5, or 10 mg of ambrisentan once daily for 12 weeks followed by 12 weeks of open-label ambrisentan. The primary end point was an improvement from baseline in 6-min walk distance (6MWD); secondary end points included Borg dyspnea index, World Health Organization (WHO) functional class, a subject global assessment, and cardiopulmonary hemodynamics.

RESULTS At 12 weeks, ambrisentan increased 6MWD (+36.1 m, $p < 0.0001$) with similar and statistically significant increases for each dose group (range, +33.9 to +38.1 m). Improvements were also observed in Borg dyspnea index, WHO functional class, subject global assessment, mean pulmonary arterial pressure (−5.2 mm Hg, $p < 0.0001$), and cardiac index (+0.33 l/min/m^2, $p < 0.0008$). Adverse events were mild and unrelated to dose, including the incidence of elevated serum aminotransferase concentrations >3 times the upper limit of normal (3.1%).

CONCLUSIONS Ambrisentan appears to improve exercise capacity, symptoms, and hemodynamics in patients with PAH. The incidence and severity of liver enzyme abnormalities appear to be low. (J Am Coll Cardiol 2005;46:529–35) © 2005 by the American College of Cardiology Foundation

Pulmonary arterial hypertension (PAH) is defined as a group of diseases characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and premature death (1). It includes idiopathic PAH (IPAH) and PAH associated with various conditions such as collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, anorexigen use, and human immunodeficiency virus infection (1,2).

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Endothelin (ET), a peptide produced primarily by vascular endothelial cells, has been characterized as a powerful vasoconstrictor and mitogen for smooth muscle (3,4). Activation of the ET system has been shown in both plasma (5) and lung tissue (6) of PAH patients, as well as in animal models of PAH (7), supporting a prominent role of ET in the pathogenesis of this condition (8).

Endothelin binds to two types of receptors, ET_A and ET_B. The ET_A receptors are found in smooth muscle cells, whereas ET_B receptors are localized on both endothelial cells and smooth muscle cells (9). Activation of ET_A and ET_B receptors on smooth muscle cells mediates the vasoconstrictive and mitogenic effects of ET (8). Stimulation of endothelial ET_B receptors promotes ET clearance and activation of nitric oxide and prostacyclin release, which induces vasodilation and antiproliferative effects (8). Selective ET_A receptor antagonism may be more beneficial than antagonism of both ET_A and ET_B receptors by inhibiting vasoconstrictive and mitogenic effects of ET_A receptor stimulation while preserving the natural vasodilator and clearance responses induced by ET through ET_B receptors.

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Abbreviations and Acronyms

6MWD = 6-min walk distance
ERA = endothelin receptor antagonist
ET = endothelin
IPAH = idiopathic pulmonary arterial hypertension
mPAP = mean pulmonary arterial pressure
PAH = pulmonary arterial hypertension
PCWP = pulmonary capillary wedge pressure
PVR = pulmonary vascular resistance
WHO = World Health Organization

To date, bosentan, an orally active, dual ET_A and ET_B receptor antagonist, is the only approved endothelin receptor antagonist (ERA) for the treatment of PAH (10). The major limitation of bosentan treatment is the elevation of serum aminotransferase concentrations to >3 times the upper limit of normal in ~12% of cases.

Ambrisentan is a potent ET_A-selective receptor antagonist with a bioavailability and half-life (9 to 15 h) that allows once-daily dosing (11). We present the results of a randomized dose-ranging study that examined the efficacy and safety of ambrisentan in patients with PAH. This study was composed of a 12-week, double-blind, fixed-dose period and a 12-week, open-label extension period.

METHODS

Study population. Male and female patients 18 years of age or older with symptomatic PAH despite treatment with anticoagulants, vasodilators, diuretics, cardiac glycosides, or supplemental oxygen for at least 4 weeks were enrolled. The PAH was either idiopathic or was associated with collagen vascular disease, anorexigen use, or human immunodeficiency virus infection. Inclusion criteria included a 6-min walk distance (6MWD) between 150 and 450 m, mean pulmonary arterial pressure (mPAP) ≥25 mm Hg, pulmonary vascular resistance (PVR) >240 dynes · s/cm^5, and pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure <15 mm Hg. Patients were excluded from the study if they had congenital heart defects, left-sided myocardial disease, valvular heart disease, significant parenchymal lung disease, chronic thromboembolic pulmonary hypertension, or portal hypertension; had received chronic prostanoid or ERA therapy within 4 weeks before study entry; or had serum aminotransferase concentrations >1.5 times the upper limit of normal. The study was conducted according to the ethical principles stated in the Declaration of Helsinki and in adherence with applicable guidelines for good clinical practice. Local ethics committees approved the protocol, and written informed consent was obtained from all patients.

Study design. The study was a randomized, double-blind, dose-controlled trial conducted in 20 centers in the U.S., Europe, and Australia. Patients were randomly assigned to receive a blinded dose of 1, 2.5, 5, or 10 mg of ambrisentan orally once daily. Patients randomized to the 1- and 2.5-mg-dose groups received their assigned dose of ambrisentan for 12 weeks. Patients randomized to the 5- or 10-mg-dose groups initially received 2.5 mg, and doses were titrated upward over several weeks to the randomized dose (Fig. 1).

Primary and secondary efficacy assessments were collected after 12 weeks of double-blind treatment. After 12 weeks, patients were unblinded and had the option to continue treatment for an additional 12 weeks (open-label extension period). During this time, the dose of ambrisentan could be adjusted based on the investigator's assessment of clinical benefit and adverse events. More than half of the patients who participated in the open-label extension period received a different dose of study drug than their randomized dose. All patients who completed the 24-week study were eligible to enter a long-term open-label study.

Outcome measures. The primary efficacy end point was a change in exercise capacity, as measured by the change from baseline in 6MWD, evaluated after 12 weeks of therapy. The secondary end points included a change from baseline at week 12 in Borg dyspnea index, World Health Organization (WHO) functional class, quality of life as assessed by a subject global assessment, and time to clinical worsening of PAH. Clinical worsening of PAH was defined by the time to first occurrence of death, all-cause hospitalizations, the addition of a new diuretic or a doubling of the dose of diuretic, or study withdrawal because of a need for other PAH therapeutic agents (defined as prostanoids, ERAs, or sildenafil). The subject global assessment was determined using a visual analog scale (12). Patients were asked the question, "How are you feeling today?" and were asked to draw a vertical mark on a 100-mm horizontal line in which zero represented very poor and 100 represented excellent. Cardiopulmonary hemodynamics were collected at baseline and week 12 in a subset of patients enrolled at pre-specified centers. Pharmacokinetics were evaluated at baseline and at week 12 in a subset of patients. Vital signs, adverse events, and clinical laboratory measurements were evaluated every two weeks for safety. The protocol stipulated that patients would receive a reduced dose or discontinued study drug if

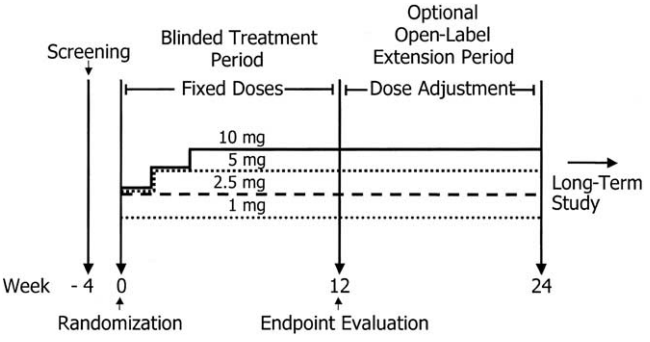

Figure 1. The study design. Subjects randomized to the 5-mg dose group received 2.5 mg for 2 weeks and 5 mg for 10 weeks. Subjects randomized to the 10-mg dose group received 2.5 mg for 2 weeks, 5 mg for 2 weeks, and 10 mg for 8 weeks. Dose adjustments were allowed during the optional open-label extension period (weeks 13 to 24).

serum aminotransferase concentrations developed that were >3 or 5 times the upper limit of normal, respectively.

Statistical analysis. All randomized patients were followed up to the end of the study and included in the analyses of efficacy and safety (intent-to-treat analysis). The null hypothesis of the study was no change from baseline to week 12 in 6MWD for a single-dose group, and a one-sample *t* test was used to test the null hypothesis for each dose. A sample size of 15 patients for a single-dose group was estimated to provide 80% power to detect a 50-m change from baseline, according to a one-sample *t* test with a type I error of 0.05 (two-sided) and a standard deviation of 69.5 m. Linear regression modeling was used to examine the null hypothesis of no linear relationship between the four doses of ambrisentan and the change from baseline in the distance walked during the 6-min walk test for each dose measured at week 12. A sample size of 60 patients was estimated to provide 80% power to detect a correlation (r) of 0.35 (an r^2 of 12%), assuming a type I error of 0.05 (two-sided).

For the primary end point, the last 6MWD recorded was used for all missing data at week 12 (last observation carried forward). For the secondary end points, no imputations for missing data were performed unless stated otherwise. The time to clinical worsening of PAH was displayed as a Kaplan-Meier curve for each dose group. Differences between curves were tested for significance by the log-rank test and by the Cox proportional hazards model (linear and logarithmic). Dose adjustments were allowed during the open-label extension period (weeks 13 to 24); therefore, the results from all dose groups during this period were combined to examine efficacy and safety. Data are reported as mean or mean ± standard error of the mean if not otherwise stated.

RESULTS

Patients. A total of 64 patients were randomized to one of four dose groups (1, 2.5, 5, and 10 mg ambrisentan). Baseline characteristics of the four dose groups were generally well matched (Table 1), including several key hemodynamic variables (Table 2). However, baseline 6MWDs indicate that the patients who received the 10-mg dose may have represented a somewhat sicker population.

Three patients discontinued the study because of adverse events during the 12-week treatment period: two patients because of sudden death (1- and 10-mg-dose groups) and one patient because of elevated serum aminotransferase concentrations (5-mg-dose group). Three patients in the 2.5-mg-dose group also discontinued: one patient because of an inclusion criteria violation (pulmonary capillary wedge pressure >15 mm Hg), one patient voluntarily withdrew, and one patient was lost to follow-up. All six patients had their last 6MWD carried forward to the 12-week assessment. Two patients (1- and 5-mg-dose groups) who completed the 12-week treatment period did not have the option to participate in the 12-week open-label extension period. One patient in the 5-mg-dose group voluntarily withdrew from the open-label extension period, and one patient in the 10-mg-dose group voluntarily discontinued from the open-label extension period because of lack of improvement.

Exercise capacity. The 6MWD improved for all dose groups combined after 12 weeks of treatment, with a mean increase from baseline of +36.1 m ($p < 0.0001$). A similar improvement was observed in all dose groups: +33.9 ($p = 0.0029$), +37.1 ($p = 0.0004$), +38.1 ($p = 0.0112$), and +35.1 ($p = 0.0080$) m for the 1-, 2.5-, 5-, and 10-mg-dose groups, respectively, and no dose-response relationship was observed (Fig. 2A). Subgroup analyses (Figs. 2B and 2C) indicate that the 6MWD increased in patients with IPAH (+39.9 m, $p < 0.0001$) as well as in patients with PAH due to other etiologies (+30.2, $p = 0.0026$) and for patients in WHO functional class II (+37.7 m, $p < 0.003$) as well as in those in WHO functional class III (+35.2, $p < 0.001$).

Table 1. Demographics and Clinical Characteristics at Baseline

Ambrisentan Dose*	1 mg (n = 16)	2.5 mg (n = 19)	5 mg (n = 16)	10 mg (n = 13)	All Doses (n = 64)
Female, n (%)	14 (87)	18 (95)	12 (75)	10 (77)	54 (84)
Age, yrs	53 ± 17	52 ± 17	48 ± 16	53 ± 12	51 ± 16
Ethnicity, n (%)					
Caucasian	11 (69)	14 (74)	10 (63)	10 (77)	45 (70)
Non-Caucasian	4 (25)	5 (26)	5 (31)	3 (23)	17 (27)
Information unavailable	1 (6)	0 (0)	1 (6)	0 (0)	2 (3)
Etiology of PAH, n (%)					
Idiopathic PAH	9 (56)	11 (60)	12 (75)	7 (54)	39 (61)
PAH associated with collagen vascular disease	7 (44)	6 (30)	2 (13)	4 (31)	19 (30)
PAH associated with anorexigen use	0 (0)	1 (5)	1 (6)	2 (15)	4 (6)
PAH associated with HIV infection	0 (0)	1 (5)	1 (6)	0 (0)	2 (3)
WHO functional class, n (%)					
II	6 (37)	6 (32)	8 (50)	3 (23)	23 (36)
III	10 (63)	13 (68)	8 (50)	10 (77)	41 (64)
6-min walk distance, m	355 ± 77	340 ± 59	378 ± 75	289 ± 91	343 ± 79

*Differences between dose groups were non-significant by Fisher's exact test and two-sample *t* test, with the exception of baseline 6-min walk distance between the 1- and 10-mg groups ($p = 0.05$) and the 5- and 10-mg groups ($p < 0.01$). Values shown are mean ± SD unless otherwise noted.

HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; WHO = World Health Organization.

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Table 2. Cardiopulmonary Hemodynamics

Ambrisentan Dose	1 mg	2.5 mg	5 mg	10 mg	All Doses
Number of patients					
Baseline§	10	9	10	5	34
Change from baseline	9	8	9	3	29
Mean cardiac index (l/min/m^2)					
Baseline	2.5 ± 0.5	2.4 ± 0.6	2.3 ± 0.6	2.5 ± 0.5	2.4 ± 0.5
Change from baseline	0.10 ± 0.31	0.41 ± 0.48*	0.47 ± 0.62*	0.37 ± 0.16†	0.33 ± 0.47*
Mean PAP (mm Hg)					
Baseline	50 ± 18	49 ± 13	47 ± 10	52 ± 11	49 ± 13
Change from baseline	−4.3 ± 4.0*	−4.3 ± 8.4	−4.3 ± 4.8*	−13.3 ± 5.1*	−5.2 ± 6.2*
Mean PVR (dyn · sec/cm^5)					
Baseline	839 ± 483	804 ± 457	881 ± 339	828 ± 416	840 ± 407
Change from baseline	−178 ± 98*	−173 ± 199*	−277 ± 261*	−345 ± 226	−226 ± 202*
Mean RAP (mm Hg)					
Baseline	7.3 ± 4.0	9.1 ± 6.1	5.2 ± 3.5	8.2 ± 2.9	7.3 ± 4.5
Change from baseline	0.89 ± 3.44	−1.13 ± 6.08	−0.44 ± 4.77	−2.67 ± 5.51	−0.45 ± 4.75

*$p < 0.05$. †$p = 0.056$. ‡n = 8 for pulmonary vascular resistance in the 1-mg-dose group, and n = 28 for all doses combined, because one patient did not have a baseline pulmonary capillary wedge pressure reading. Values shown are mean ± SD.
PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure.

Improvements in exercise capacity were maintained and continued to increase up to 24 weeks: +50.2 ($p < 0.0001$), +50.9 ($p < 0.0001$), and +54.2 m ($p < 0.0001$) at 16, 20, and 24 weeks, respectively (Fig. 3). At week 24, there was a larger improvement in 6MWD for IPAH patients compared with patients with other etiologies (+64.3 and +38.5 m, respectively; $p = 0.05$, two-sample *t* test), whereas similar improvement continued to be observed for WHO functional class II and class III patients (+58.3 and +51.9 m, respectively).

At week 12, there was a mean improvement from baseline (as indicated by a decrease) in the Borg dyspnea index score of −0.6 ± 0.5, −0.9 ± 0.4, −1.0 ± 0.6, and −1.0 ± 0.6 for the 1-, 2.5-, 5-, and 10-mg-dose groups, respectively. The Borg dyspnea index score at baseline for all dose groups combined was 4.0 ± 0.3, which improved by −0.9 ± 0.3 ($p = 0.0015$) at week 12 and was maintained through week 24 (−1.3 ± 0.3, $p < 0.0001$).

WHO functional class. Improvements in WHO functional class were observed for all dose groups, yet no dose-response relationship was observed. At baseline, 64% of the patients were WHO class III with the remainder being WHO class II. By week 12, 38% of patients were WHO class III, 50% were WHO class II, and 12% were WHO class I (Fig. 4). Eighteen patients (36.2%, 95% confidence interval 25.7% to 46.7%) improved one or more WHO functional classes, whereas only two patients (3.4%, 95% confidence interval −9.4% to 16.2%) worsened at week 12. The improvements in WHO functional class continued to be maintained through week 24.

Clinical worsening. By week 12, clinical worsening of PAH was observed in 13 of 64 patients (20.3%). In 6 (46.2%) of the 13 patients in whom clinical worsening of PAH developed, as defined in the protocol, it was caused by an increase of the dose of diuretic. There was no correlation between the dose of ambrisentan and the incidence of increased diuretics. Neither log-rank analysis nor Cox proportional hazards models indicated any significant difference in times to clinical worsening of PAH among dose groups. During the open-label extension period, there were eight patients in whom clinical worsening developed; all but three cases were attributable to an increased dose of diuretics.

Subject global assessment. At baseline, the mean subject global assessment score for all dose groups combined was 56.4 ± 2.6 mm, which improved by +11.3 ± 2.4 mm ($p < 0.0001$) at week 12. When missing data at week 12 were replaced with a subject global assessment score of 0 mm (maximum penalty), the subject global assessment improved from baseline by 23.2% ($p = 0.0232$, one-sample *t* test) for all dose groups combined. No differences among dose groups were observed. In the open-label extension period, the improvement was maintained up to 24 weeks (+12.1 ± 2.7 mm, $p < 0.0001$).

Hemodynamics. Cardiopulmonary hemodynamics at baseline and week 12 for a subset of patients are reported in Table 2. Mean pulmonary artery pressure decreased in all dose groups combined as well as for the 1-, 5-, and 10-mg-dose groups. Cardiac index increased in all dose groups combined, as well as for the 2.5- and 5-mg-dose groups. Pulmonary vascular resistance decreased in all dose groups combined, as well as for the 1-, 2.5-, and 5-mg-dose groups. A non-significant trend toward reduction in right atrial pressure was observed, with the exception of the 1-mg-dose group.

Pharmacokinetics. Single-dose and steady-state plasma concentration time profiles were biphasic and steady-state pharmacokinetics were predictable based on data from single doses. The onset of absorption was rapid, with a maximum plasma concentration at steady-state that ranged from 111 to 1,223 ng/ml occurring 1.7 to 3.3 h after dosing and a mean elimination half-life at steady-state that ranged from 9 to 15 h.

Safety and tolerability. The most frequently reported adverse events during the 12-week blinded treatment period

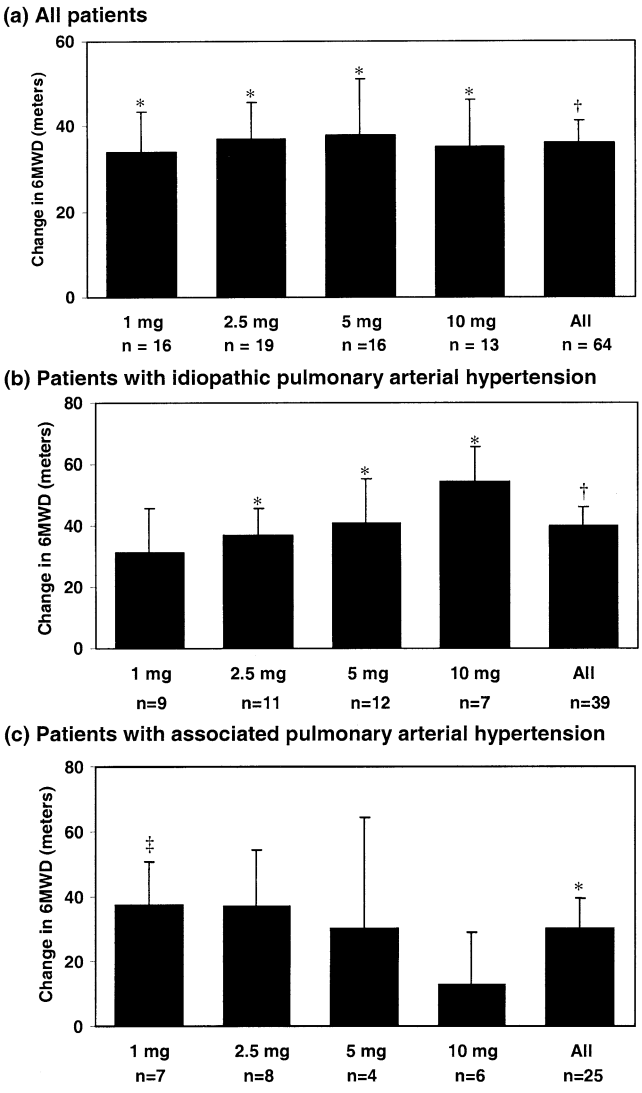

Figure 2. **(A)** Mean change from baseline in 6-min walk distance (6MWD) for all patients at week 12 for the 1-, 2.5-, 5-, and 10-mg-dose groups and for all dose groups combined. **(B)** Mean change from baseline in 6MWD for idiopathic pulmonary arterial hypertension patients at week 12 for the 1-, 2.5-, 5-, and 10-mg-dose groups and for all dose groups combined. **(C)** Mean change from baseline in 6MWD for patients with pulmonary arterial hypertension associated with collagen vascular disease, anorexigen use, or human immunodeficiency virus infection at week 12 for the 1-, 2.5-, 5-, and 10-mg-dose groups and for all dose groups combined. *$p < 0.02$, †$p < 0.001$, ‡$p < 0.03$.

were peripheral edema (25.0%), nasal congestion (18.8%), upper respiratory tract infection (18.8%), headache (15.6%), flushing (12.5%), and nausea (12.5%). No clinically meaningful differences among the four doses were observed for the total number of adverse events, the incidence of adverse events per patient, adverse event severity, or relationship to study drug. Seven patients experienced serious adverse events during the 12-week blinded treatment period, including two sudden deaths (1- and 10-mg-dose groups). In both cases, the investigator judged the death not related to the study drug.

During the 24-week study (Table 3), in one patient (5-mg-dose group), serum aminotransferase concentrations

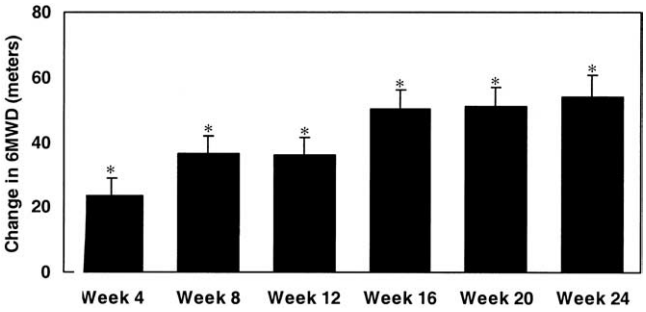

Figure 3. Mean change from baseline in 6-min walk distance (6MWD) for all dose group combined (n = 64) up to 24 weeks. **Error bars** indicate standard error of the mean. *$p < 0.001$.

>8 times the upper limit of normal developed, but the serum aminotransferase concentrations returned to the normal range within 6 weeks of drug discontinuation. In a second patient (5-mg-dose group), isolated aspartate aminotransferase concentrations >3 times the upper limit of normal developed that resulted in dose reduction and eventual discontinuation of drug during a separate long-term study (week 28). This patient was also receiving concomitant human immunodeficiency virus therapy. Two patients in the 2.5-mg-dose group had isolated elevations >3 times the upper limit of normal that were unconfirmed on re-testing and required no change in treatment. By the end of the open-label extension period (week 24), 48% of the patients were receiving a dose of 10 mg; in none of these patients did serum aminotransferase concentrations >3 times the upper limit of normal develop.

A mean reduction of 0.8 g/dl of hemoglobin concentration was observed at week 12 in all dose groups combined, but no further decreases were observed in the open-label extension period. No clinically relevant changes were observed for prothrombin time, international normalized ratio, or dose of anticoagulation therapy.

DISCUSSION

This trial has shown that ambrisentan, an ET_A-selective receptor antagonist, seems to improve exercise capacity, symptoms, and hemodynamics in patients with PAH. The observed improvements in exercise capacity and hemodynamics seem to be comparable with those achieved by other

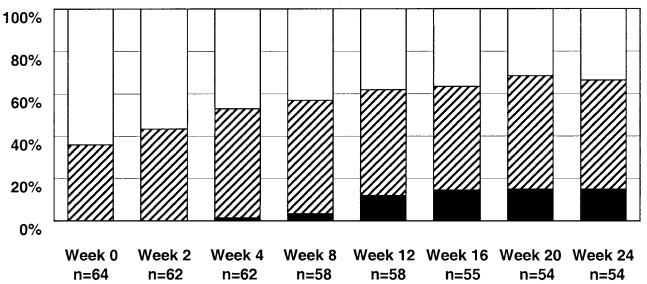

Figure 4. Change from baseline in World Health Organization functional class for all dose groups combined of ambrisentan up to 24 weeks. Higher classes indicate a greater severity of disease. **Black bars** = class I; **ruled bars** = class II; **open bars** = class III.

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Table 3. Incidence and Severity of Aminotransferase Abnormalities

Ambrisentan Dose	1 mg (n = 16)	2.5 mg (n = 19)	5 mg (n = 16)	10 mg (n = 13)	All Doses (n = 64)
>3 and ≤5 times the upper limit of normal, n (%)	0 (0)	0 (0)	1 (6.2)	0 (0)	1 (1.6)
>5 and ≤8 times the upper limit of normal, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
>8 times the upper limit of normal, n (%)	0 (0)	0 (0)	1 (6.2)	0 (0)	1 (1.6)

ERAs in similar patient populations (13), even if the lack of comparison with a placebo-treated group represents a limitation of this study (10,14). However, in the majority of randomized controlled trials performed in PAH, a deterioration of some extent has been invariably observed in both exercise capacity and hemodynamics in placebo-treated patients (15), resulting in an amplification of the treatment effect. The sustained efficacy on exercise capacity observed at week 24 suggests that the results seen in this trial were not caused by a placebo effect; however, we cannot exclude a placebo effect on more subjective parameters such as WHO class and subject global assessment.

No dose-response for efficacy as assessed by the 6MWD, WHO functional class, time to clinical worsening, or hemodynamics was observed in this study. A possible explanation for the lack of a clear dose-response may include a significant ET-receptor occupancy for a wide range of doses and plasma drug concentrations. Alternatively, the lack of a dose-response may be attributable to the small sample size of the population studied. Of note, little dose-response has been observed in other ERA studies in PAH—the BREATHE-1 study (10) showed a non-statistically significant trend toward a larger increase in 6MWD with the higher dose of bosentan, whereas no dose-response was observed for 6MWD in the sitaxsentan STRIDE-1 study (14). Furthermore, no differences were observed in the STRIDE-1 study for the hemodynamic effects of two doses of sitaxsentan. In contrast, data from the 5- and 10-mg ambrisentan dose groups suggest a better hemodynamic effect compared with the two lower doses; however, the number of patients evaluated was small and the difference may be attributable to chance.

The dose escalation scheme in the randomized part of this study resulted in a longer duration of exposure before the assessment of the efficacy end points for the 1- and 2.5-mg doses (12 weeks) as compared with the 5-mg (10 weeks) and 10-mg (8 weeks) doses. It is possible that these disparities may have prevented the detection of meaningful differences among dose groups.

The improvement in 6MWD observed at 12 weeks (+36.1 m) tended to increase further up to 24 weeks when dose adjustments were allowed, reaching a mean increase of +54.2 m. The larger response observed at week 24 in patients with IPAH as compared with the other PAH etiologies (mainly scleroderma) has been reported with the dual ERA bosentan (10,14); however, it is worth noting that the improvement observed in patients with associated PAH in this study was not caused by a placebo deterioration, as was reported in the BREATHE-1 study (10). It is also interesting to note that WHO functional class II patients respond similarly to treatment with ambrisentan as WHO functional class III patients (+37.7 m and +35.2, respectively) despite a statistically significant difference in 6MWD between these two groups at baseline (390 m and 316 m, respectively; $p = 0.0002$). This lack of a "ceiling effect" is in contrast to what was reported in a previous trial with another ET_A-selective receptor antagonist (14).

The additional improvement of exercise capacity beyond the first 12 weeks of treatment is difficult to explain by the higher doses received in the open-label extension period because of the lack of a dose-response relationship in the preceding period. One possibility is that the number of patients per dose group during the first 12 weeks was too small to observe a clear dose-response, whereas during the second 12 weeks nearly three-quarters of all patients were receiving the two highest doses. In addition, a total of 56 patients continued treatment in the optional open-label extension period, which may constitute a selection of the best responders to the treatment. However, an increase in exercise capacity beyond the first months of therapy has also been reported with the dual ERA bosentan (16) and may represent a characteristic of this class of drugs that is associated with inhibition of smooth muscle cell proliferation and vascular remodeling.

An explanation for the tendency to increase the dose of ambrisentan during the open-label part of the study is not clear. One possible reason could be the attempt of physicians to further improve the exercise capacity of those patients who were tolerating ambrisentan with minimal adverse events.

Elevations in serum aminotransferase concentrations >3 times the upper limit of normal were observed in two patients (3.1%) receiving the 5-mg dose. No patient developed serum aminotransferase concentrations >3 times the upper limit of normal at the highest dose tested (10 mg), even when nearly half of the patients received the 10-mg dose during the open-label extension period. Furthermore, in only one patient (1.6%) in this 24-week study did aminotransferase concentrations >8 times the upper limit of normal that required discontinuation of study drug develop. This low overall incidence and severity of serum aminotransferase abnormalities was not dose-dependent, in contrast to previous studies with bosentan (12% and 14% after 125- and 250-mg b.i.d. dose, respectively) (10) and sitaxsentan (5% and 21% after 100- and 300-mg once-daily dose, respectively) (14).

Clinical worsening of PAH and mortality in this study were similar to those observed in other randomized clinical

trials in this patient population (15). Interestingly, the great majority of worsening PAH in this study was characterized by increases of diuretic dose (as defined in the study protocol). This phenomenon may be related to the occurrence of fluid retention and peripheral edema—a common adverse effect of ERAs (14), and not necessarily associated with worsening of PAH. Also, although the incidence of other clinical adverse events was as expected with this class of drug (10), it is important to note that no drug interactions with warfarin-type anticoagulant treatment were observed (14).

In summary, ambrisentan, an ET_A-selective receptor antagonist, seems to improve exercise capacity, symptoms, and hemodynamics in patients with WHO class II to III PAH. Ambrisentan may have a very favorable efficacy-to-safety ratio in patients with PAH, including a low incidence and severity of serum aminotransferase abnormalities that does not seem to be dose-dependent. Phase III placebo-controlled trials are currently ongoing to confirm these initial results.

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APPENDIX

For a list of the additional members of the Ambrisentan PAH Study Group, please see the online version of this article.